

 **Using Estradiol Cypionate (ECP®) vs. GnRH in Controlled A.I.-Breeding Programs**

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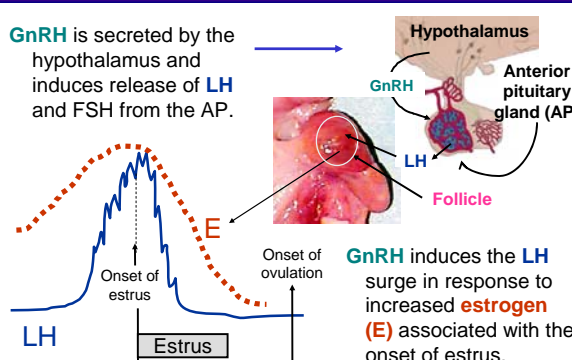
 RESEARCH & EXTENSION

Why Substitute Estrogen for GnRH?

- Estrogen induces:
 - Sexual behavior--estrus
 - Uterine tone
 - Secretion of mucus
- Cows may be somewhat easier to inseminate at timed AI.
- Increased estrus activity has positive psychological effects on those inseminating cows.
- Estrogen is significantly less costly.

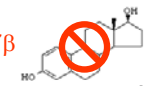
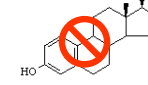
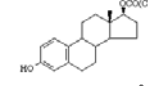
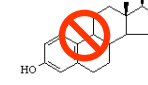
How Do Estrogen and GnRH Work?

GnRH is secreted by the hypothalamus and induces release of LH and FSH from the AP.



GnRH induces the LH surge in response to increased **estrogen (E)** associated with the onset of estrus.

Estrogens

Estradiol-17 β		Principal estrogen secreted by the follicle
Estradiol benzoate		Mimicks estradiol-17 β most closely (half-life nearly equal)
Estradiol cypionate		Longer-acting estrogen (sold as ECP®)
Estradiol valerate		Longest-acting estrogen; was part of Syncro-Mate B® estrus-synchronization protocol (not available)

Extra Label Use of Drugs

- Extra label use means a drug is used for purposes NOT listed as one of its Indications on the bottle label or bottle insert.
- For example, the label for each GnRH product indicates that its approved use is for the treatment of ovarian follicular cysts.
- Use of GnRH in any estrus-synchronization or ovulation control program is considered to be an **extra label** use.

CYSTORELIN®
Factrel®
FERTAGYL®
OvaCyst®

Extra Label Use of Drugs


- GnRH products have therapeutic approvals for use in cattle in the U.S.
- Strict interpretation of Animal Medicinal Drug Use Clarification Act (AMDUCA) is that GnRH products cannot be used for production purposes in cattle.
- However, GnRH products are being used extensively for estrus-synchronization programs by veterinarians and academic researchers who have published their results in scientific journals and producer press.

Extra Label Use of Drugs

- GnRH is a peptide (very small protein with a short blood half life) with no known health concerns.
- FDA must have minimal concerns regarding use of GnRH products in estrus-synchronization programs because no known prosecutions have been initiated.



Illegal Use of Drugs and Compounding of Products

- Estradiol benzoate (EB) has no human or animal approval in the U.S.
- Strict interpretation of AMDUCA is that EB cannot be used for production purposes in cattle.
- Therefore, use of EB in cattle for estrus-synchronization programs is illegal. 
- Use of EB also is illegal when compounded with any other approved product.
- Use of the Eazi-Breed™ CIDR® Cattle insert plus Lutalyse® is an **approved** compounding of products.

What Estrogen is Approved?

- Estradiol cypionate (ECP) has a therapeutic label for use in cattle in the U.S.
- It is the only estrogen approved for use in cattle is ECP® (Pharmacia)
- ECP has multiple label indications including “to correct anestrus [absence of heat period] in the absence of follicular cysts” at 3 to 5 mg doses.



Use of ECP in Breeding Programs

- Strict interpretation of AMDUCA is that ECP cannot be used for production purposes in cattle.
- Because ECP is an estrogen, it is of concern to the U.S. Food and Drug Administration-Center for Veterinary Medicine relative to human health and safety.

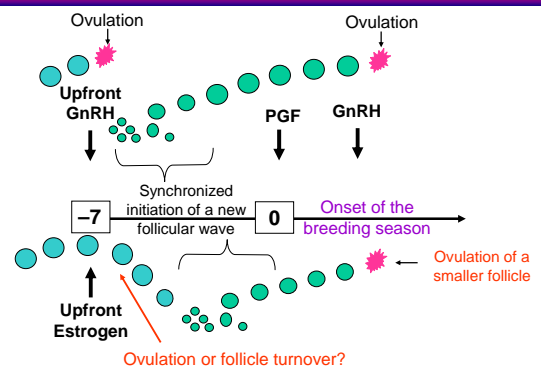


Use of ECP in Breeding Programs

- ECP is being used extensively for estrus-synchronization programs by veterinarians and academic researchers who have published their results in scientific journals and producer press.
- FDA has not initiated prosecutions of either researchers or veterinarians using ECP in cattle estrus-synchronization programs.



Follicle Control

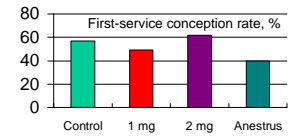


What Must Estrogen Do To Replace GnRH in Breeding Programs?

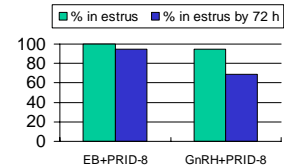
- Estrogen must induce **upfront follicle turnover in a synchronization program in cycling cows.**
- Estrogen must induce **upfront ovulation in anestrous cows.**
- Estrogen must induce **ovulation after PGF.**
- Estrogen must **not** produce “hyper-estrus” activity to prevent injury of cows caused by excessive riding and standing behavior.
- Estrogen must be **easy to administer.**

Upfront Follicular Control?: Cycling

- Upfront EB (1 vs. 2 mg) at CIDR-7 insertion was effective for lactating cycling cows (Day et al., 2000).



- Upfront EB vs. GnRH at PRID-8 insertion was effective in cycling replacement heifers (Lane et al., 2001).



Upfront Follicular Control?: Anestrus

- Use of EB at 0.5 or 1.0 mg dose at the time of CIDR insertion did not induce ovulation effectively in seasonally **anestrous** dairy cattle (Verkerk et al., 1998). **Beef cattle?**
- EB + CIDR reduced formation of persistent follicles in lactating **anestrous** dairy cows, but delayed follicular development in some **anestrous** cows (Rhodes et al., 2002). **Beef cattle?**
- Immature dominant follicles in **suckled anestrous** cows were **less likely to ovulate** after EB (Burke et al., 2001).

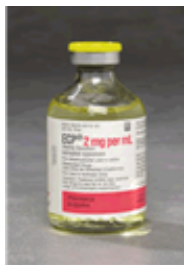
Ovulation after PGF-induced Luteolysis?

Response	Kansas	Florida
ECP to LH surge, h	19.1 ± 2.6	
Onset of estrus after ECP , h	27.8 ± 3.2	29.0 ± 1.8
Duration of estrus, h	6.9 ± 0.7	12.5 ± 1.8
No. of standing events	17.1 ± 5.2	20.3 ± 2.8
Total standing timed, sec	36.3 ± 12	47.6 ± 7.5
Ovulation after estrus onset, h	29.9 ± 2.4	27.5 ± 1.1
Ovulation after ECP , h	60.0 ± 1.8	55.4 ± 2.7

After luteolysis, ECP induces ovulation in lactating dairy cows and in replacement heifers (Lopes et al., 2000).

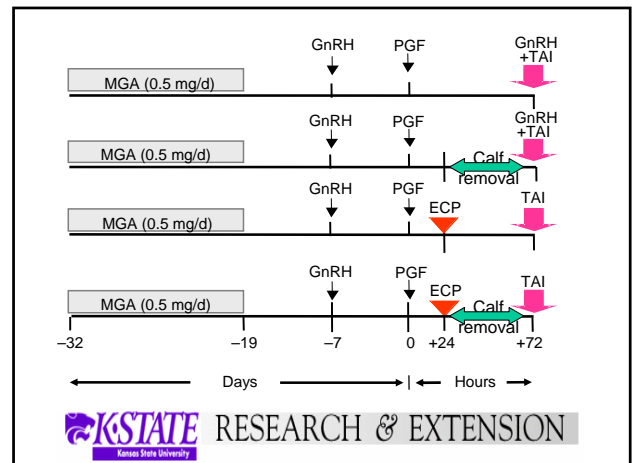
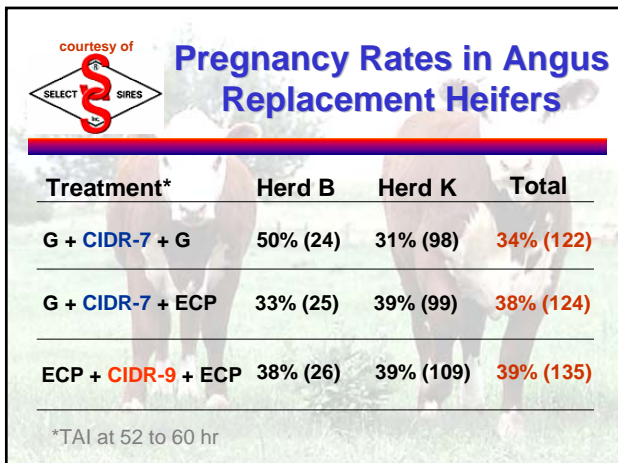
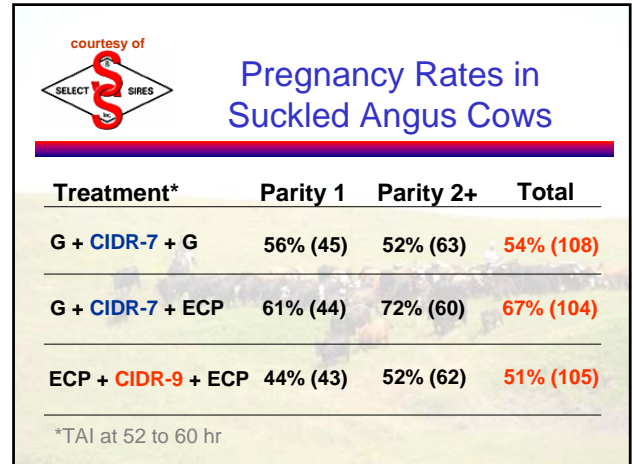
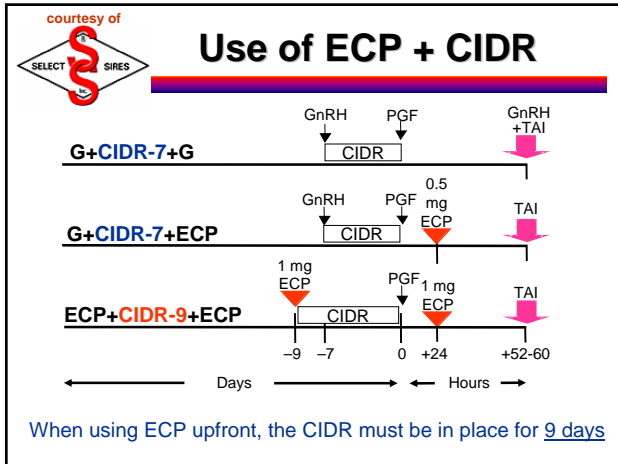
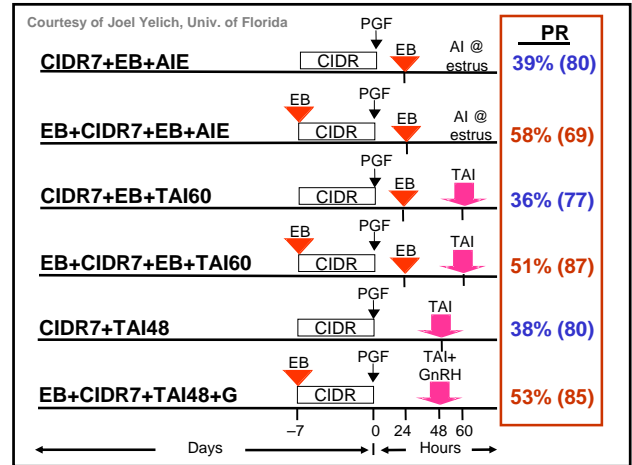
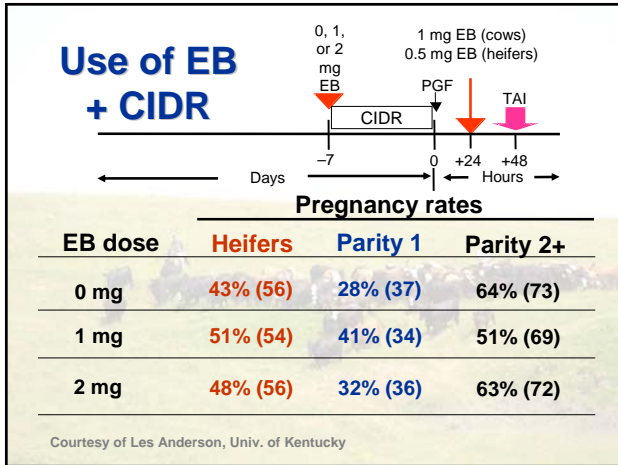
Easily Administered?

- ECP is dosed at 2 mg per mL.
- A small syringe is required to deliver 1 mg of ECP i.m. in a volume of 0.5 mL (0.5 cc).
- When injecting cows, follow Beef Quality Assurance (BQA) guidelines to reduce carcass bruising and injection site lesions (i.e., use neck injection sites).



EAZI-BREED CIDR® Cattle Insert





ECP vs. GnRH

Calf removal	ECP	GnRH	Total
Yes	49% (94)	51% (97)	50%* (191)
No	51% (90)	38% (88)	44% (178)
Total	50%+ (184)	44% (185)	47% (369)

*Different (P<0.05) from no calf removal.

+Different (P<0.05) from GnRH.

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Summary

- ECP is an alternative to GnRH for upfront follicle control, but may not be as effective as GnRH for anestrous cows.
- If ECP is used upfront at CIDR insertion, the CIDR must be in place for 9 days, rather than 7 days when using GnRH.
- After CIDR removal, ECP is an alternative to GnRH after luteolysis for TAI systems.
- Pregnancy rates to TAI tended to be greater in suckled cows when treated after PGF with ECP than GnRH.

Resynchronization of Estrus

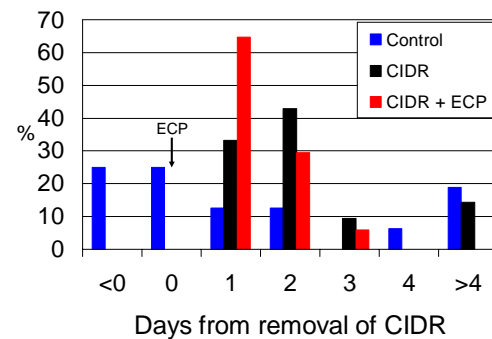
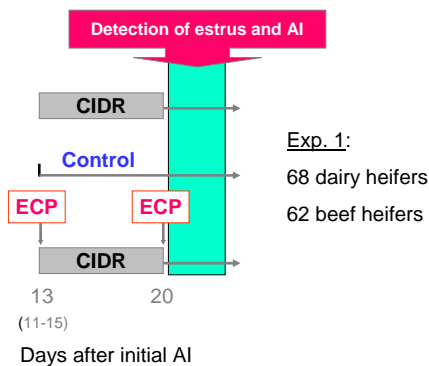
- Increase opportunity for more A.I.-sired calves
- Take full advantage of previous synchrony with little additional cost
- Facilitate heat detection of first eligible heat after A.I.

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Protocols for Resynchronization of Estrus

- Previously used progestin-releasing inserts or implants
- Feeding of a progestin (e.g., MGA)
- Combination progestins with estrogen injections
- Use of Ovsynch and Heatsynch

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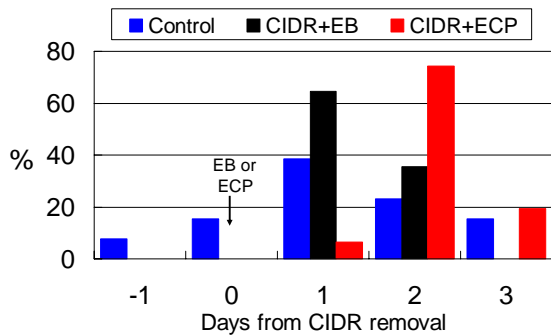
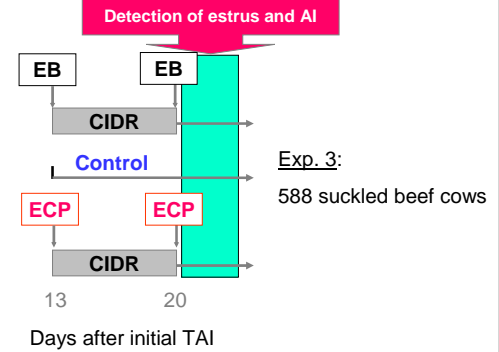


Stevenson et al. 2003. J. Anim. Sci. In press.

Exp. 1. Reproductive Traits

Item	Con	CIDR	CIDR + ECP
No. of heifers	44	42	44
PR after 1 st A.I.	53%	47%	60%
Return 18-26 days	73%	84%	90%
CR of repeat A.I.	60%	33%	35%
26-day PR	72%	60%	73%

Stevenson et al. 2003. J. Anim. Sci. In press.



Stevenson et al. 2003. J. Anim. Sci. In press.

Exp. 2. Reproductive Traits

Item	Con	CIDR + EB	CIDR + ECP
No. of cows	292	151	145
PR after 1 st A.I.	52%	44%	52%
Return 20-23 days	29%	84%	65%
CR of repeat A.I.	65%	52%	65%

Stevenson et al. 2003. J. Anim. Sci. In press.

Summary

Resynchronization of repeat estrus:

- Had no negative effect on established pregnancies.
- Increased synchrony of repeat estrus.
- Tended to reduce resynchronized conception rates after resynchronization in dairy and beef heifers .
- Produced normal conception rates at the resynchronized estrus in suckled beef cows when ECP + CIDR were used.

Thanks to the following for their financial or product support:



• Select Sires

- Pharmacia Animal Health
- Fort Dodge Animal Health
- Intervet
- Merial



